PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/820,486 Confirmation No. 7395

Applicant : Zhi-Jian Yu

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Examiner : Brown, Courtney A.

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Title: Cetylpyridinium Chloride as an Antimicrobial Agent in Ophthalmic Compositions

Declaration under 37 CFR §1.132

COMMISSIONER FOR PATENTS
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SIR:

I, Zhi-Jian Yu, Ph.D., hereby make the following declaration:

1 I received a Ph.D. in Physical Chemistry from Beijing University, China, in July, 1987.

2 From 9/87 – 5/89, I was a Postdoctoral Fellow at the INSTITUTE OF CHEMISTRY, ACADEMIA SINICA, Beijing, China.

3 From 6/89 – 5/94, I was a Postdoctoral Fellow in the Department of Chemical Engineering at AUBURN UNIVERSITY, Auburn, Alabama, researching the surface chemistry of solvent extraction of heavy metals.

4 Other professional positions prior to my current one are described in the C.V. attached hereto.

5 From 6/02 – Present, I have been employed as a Principal Scientist, ABBOTT MEDICAL OPTICS INC, Santa Ana, CA (formerly Advanced Medical Optics, Inc.), conducting research and development of products for dry eye treatment and contact lens cleaning and disinfection.

6 I have read the subject patent application, the rejections in the Office Action dated October 28, 2008, and the prior art cited against the invention: Tuse et al., (US 6,482,799), Araki et al. (US 2003/0203849), Zhao (US 2003/0228393), Dykens et al. (US 2003/0105167) and Huth (US 2004/0120916).). I am fully familiar with the field of technology embraced by this patent application and the cited prior art.

7 The invention relates to an aqueous solution for contact lens care containing cetylpyridinium chloride (CPC) with an upper limit of about 9.5 ppm. When using CPC, it is critical to select the right surfactant or it will inactivate the antimicrobial activity. This Declaration shows that the non-ionic surfactant POP-POE is effective without reducing the antimicrobial properties of CPC. As a result, the amount of CPC in the solution can be surprisingly low.

8 Araki et al mentions that POP-POE block copolymers can function as gelling agents, among a group of cellulosic gelling agents, not surfactants. A person of

ordinary skill in the art would not focus on the POP-POE over the disclosed cellulosic gelling agents, for purposes of the present invention.

9 POP-POE as used in the present invention is significantly below the level that would be required to 'gel'. In fact, we would like to avoid 'gelling' completely. As such, one of ordinary skill in the art would not have looked at the teaching of Araki to formulate a multi-purpose contact lens solution.

10 At gelling concentrations, this would have taught away from the formulation of a MPS. Gelling occurs at very high POP-PEO concentration. For example, the viscosity of a 10% w/v Pluronic F87 solution is only 4 cps. The viscosity of 10% Tetronic 904 is 2.66 cps. That is, both solutions are watery. A gelling solution normally has a viscosity of more than 100 - 10,000cps. Therefore, > 10% w/v of POP-PEO is required as a gelling agent.

11 POP-POE as a gelling agent has several problems.

i. Inactivation of CPC antimicrobial activity due to too high POP-PEO concentration. This can also be seen from Table 4. When Pluronic F87 increases from a detergent level of 0.05% to 0.2%, the AME activity decreases to a marginal level as a stand-alone MPS. At the POP-PEO concentration of > 10%, CPC will be inactive as a disinfecting agent.

ii. It will excessively increase the retention time of CPC on the cornea due to the composition's high viscosity, which would hold the CPC in place over the cornea, causing Corneal toxicity such as cornea staining and irritation.

iii. When the composition is evaporated during normal usage, a thick film would form in the lens case causing microbes to be trapped underneath the film and separated from the disinfecting solution.

iv. Any gel residue left on a contact lens (it is standard for MPS residue to be left on the lens when it is inserted in the eye) would be too irritating and cytotoxic.

12 The table below contains the results of comparative experiments conducted as described on pages 21 – 25 of the specification. One can see that CPC/POP-POE has greater antimicrobial efficacy than CPC with other surfactants. Pluronic F87 and Tetronic 904 are PPO-PEO surfactants, and cause no noticeable loss in the antimicrobial activity of CPC at the tested concentration. In fact, Pluronic F87 and Tetronic 904 enhanced the activity against C albicans 10231 when compared with no surfactant in solution (although I expect it to decrease above 1% w/w). In contrast, TPGS, Tween 80 and Cremophor-40, which are non-PPO-PEO surfactants, caused almost total loss in antibacterial efficacy.

	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
TPGS		0.10				
Tween 80			0.10			
Cremophor 40				0.10		
Pluronic F87					0.10	
Tetronic 904						0.10
CPC	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
Boric acid	0.60	0.60	0.60	0.60	0.60	0.60
Sodium Borate-10H20	0.15	0.15	0.15	0.15	0.15	0.15
NaCl	0.45	0.45	0.45	0.45	0.45	0.45
EDTA	0.05	0.05	0.05	0.05	0.05	0.05
	Log drops @ 6 hours					
S.marcescens 13880	>4.38	0.15	-0.01	0.07	>4.38	>4.38
S.aureus 6358	>4.42	0.11	0	0.1	>4.42	>4.42

P.aeruginosa 9027	>4.3	1.3	0.2	0.2	>4.3	>4.3
C. albicans 10231	2.8	0	-0.1	-0.2	>4.1	>4.1
F.solani 30361	>4.0	0.2	0.3	0.4	>4.0	>4.0

13 I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 03/30/09

By: _____
Zhi-Jian Yu, Ph.D.,

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EXPERIENCE

6/02 – Present **ABBOTT MEDICAL OPTICS INC,** Santa Ana, CA

Principal Scientist

- Conduct research and development of products for dry eye treatment and contact lens cleaning and disinfection.

11/97 – 6/02 **METREX RESEARCH CORPORATION,** Orange, CA

Senior Research Scientist

- Developed **Caviwipes® and Metriwipes®** for hard surface disinfection.
- Developed **Compliance™**, a high level disinfectant and sterilant for medical instruments
- Developed **Metrilube®, Metriwash®,** and **EmPower™** for medical instrument pre-cleaning.

8/96 – 11/97 **CUBIST PHARMACEUTICALS INC.,** Cambridge, MA

Research Scientist

- Designed and formulated new generation antibiotics for MRSA and VRE.
- Developed long-lasting aerosol formulations for respiratory tract infection treatment..
- Developed I.V. injectable formulation for water insoluble antibiotics using cyclodextrins as drug carriers.

3/95 –7/96 **ALLERGAN INC.,** Irvine, CA

Research Scientist

- Conducted ophthalmic product development for dry eye treatment.

5/94 – 3/95 **NYCOMED SALUTAR INC.,** Sunnyvale, CA

Research Scientist

- Researched drug encapsulation, and nano-particle coating and developed parenteral diagnostic imaging drugs.

6/89 – 5/94 **AUBURN UNIVERSITY**, Auburn, Alabama
Department of Chemical Engineering

Postdoctoral Fellow

- Researched the surface chemistry of solvent extraction of heavy metals.

9/87 – 5/89 **INSTITUTE OF CHEMISTRY, ACADEMIA SINICA**, Beijing, China

Postdoctoral Fellow

- Researched static and time resolved fluorescence in surfactant solutions.

EDUCATION **Ph.D.** Physical Chemistry, Beijing University, China, July, 1987.
MS. Physical Chemistry, Beijing University, China, July, 1984.
BS. Chemistry, Beijing University, China, April, 1982.

HONORS **1988** Distinguished Young Chemist Award by Chinese Chemical Society and Chinese National Science Foundation.

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